ANEMIA, IRON DEFICIENCY, AND IRON DEFICIENCY ANEMIA

Anemia is one of the most widespread public health problems, especially in developing countries, and has important health and welfare, social, and economic consequences. These include impaired cognitive development, reduced physical work capacity, and in severe cases increased risk of mortality, particularly during the perinatal period. There is also evidence that anemia may result in reduced growth and increased morbidity. Given the magnitude of the problem, greater efforts are needed to develop and implement programs both to prevent and to control anemia. In program development, it is essential to understand the differences between anemia, iron deficiency, and iron deficiency anemia, and to recognize that anemia can result both from nutrition-related causes and from inflammatory/infectious disease, as well as from blood loss.

Anemia can result from nutrition-related causes, in particular iron deficiency, from inflammatory/ infectious disease, and from blood loss.

This statement was prepared by Dr. Penelope Nestel and Dr. Lena Davidsson. It was reviewed by the INACG Steering Committee.

What is anemia?

Anemia is defined as a hemoglobin concentration lower than the established cutoff defined by the World Health Organization. This cutoff figure ranges from 110 g/L for pregnant women and for children 6 months–5 years of age, to 120 g/L for nonpregnant women, to 130 g/L for men.[1] In addition to sex, age, and pregnancy status, other factors influence the cutoff values for hemoglobin concentration. These include altitude, race, and whether the individual smokes.[1] Anemia can be diagnosed by analyzing the hemoglobin concentration in blood or by measuring the proportion of red blood cells in whole blood (hematocrit).

Hemoglobin is an iron-containing protein in red blood cells that carries oxygen from the lungs to cells throughout the body. Without sufficient oxygen the physical capacity of individuals is reduced.

Iron deficiency and iron deficiency anemia

With adequate nutrition, a reserve of iron is stored in tissues and is used when insufficient iron is absorbed, for example, when dietary intakes are inadequate or bioavailability is low.* The size of the body's iron reserve, mostly in the liver, is therefore an index of iron nutritional status. Iron deficiency occurs in three sequentially developing stages.

For diagnostic purposes, the critical stages of inadequate iron nutriture are:

Depleted iron stores: Iron stores are absent but the hemoglobin concentration remains above the anemia cutoff.

Iron deficiency anemia: Iron stores are absent and/or the transport of iron is reduced. The hemoglobin concentration falls below the cutoff.

The first stage is ***depleted iron stores.*** This occurs when the body no longer has any stored iron but the hemoglobin concentration remains above the established cutoff levels. A depleted iron store is defined by a low serum ferritin concentration (<12 µg/L). It is important to note that because ferritin is an acute-phase reactant, its concentration in the blood increases in the presence of subclinical and clinical inflammatory/infectious diseases; thus, it cannot be used to accurately assess depleted iron stores in settings where poor health is common.

The second stage is known as ***iron-deficient erythropoiesis***. Developing red blood cells have the greatest need for iron, and in this stage the reduced transport of iron is associated with the development of iron-deficient erythropoiesis. However, the hemoglo-

* Bioavailability refers to the degree to which iron is available for absorption in the gut and utilized for normal metabolic functions.

bin concentration remains above the established cut off levels. This condition is characterized by an increase in the transferrin receptor concentration and increased free protoporphyrin in red blood cells.

The third and most severe form of iron deficiency is ***iron deficiency anemia*** (IDA). IDA develops when the iron supply is inadequate for hemoglobin synthesis, resulting in hemoglobin concentrations below the established cutoff levels. To diagnose IDA, measurements of iron deficiency as well as hemoglobin concentration are needed.

For practical purposes, the first and second stages are often referred to collectively as ***iron deficiency.***

Other causes of anemia

Other nutrient deficiencies have been associated with anemia. These include deficiencies of vitamins A, B-6, and B-12, riboflavin, and folic acid,[2] although not all of the causal pathways have been clearly established.

Besides specific nutrient deficiencies, general infections and chronic diseases including HIV/AIDS, as well as blood loss, can cause anemia. For example, the risk of anemia increases when individuals are exposed to malaria and helminth infections. There are also many other, rarer causes of anemia, the most common being genetic disorders such as the thalassemias.

Malaria, especially from the protozoan ***Plasmodium falciparum***, causes anemia by rupturing red blood cells and by suppressing the production of new red blood cells. Malaria does not, however, cause iron deficiency, because much of the iron in hemoglobin released from the ruptured cells stays in the body.

Helminths such as hookworms and flukes such as schistosomes can cause blood loss and therefore iron loss. Adult hookworms attach themselves to the gut wall, where the mature larvae and adult worms ingest both the gut wall and blood. Hookworms change feeding sites every 4–6 hours and during feeding secrete anticoagulant, resulting in secondary blood loss from the damaged gut wall after the worms have stopped feeding. The number of adult hookworms and the fecal egg count, which is an indirect estimate of the number of worms, are strongly correlated with the amount of blood lost, which if chronic can result in iron deficiency anemia.

The nematode ***Trichuris trichiura*** can cause anemia when the worm burden is heavy. Heavy infections also cause inflammation and dysentery, which in turn can cause further blood loss.

The trematode ***Schistosoma haematobium*** can cause significant urinary blood loss in severe infection. The effect of this blood loss can be significant even in moderate infections if the person is

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young and already anemic. The eggs are wedged into capillaries by female worms when they are laid, and the mechanical movements of the body push them into the bladder wall. The emerging eggs rupture the bladder wall, causing blood to leak into the bladder. With ***Schistosoma mansoni***, emerging eggs rupture the intestinal lining, resulting in the leakage of blood and other fluids and nutrients into the lumen.

Anemia from iron deficiency versus other causes

A study of Zanzibari schoolchildren estimated that if hookworm infection could be eradicated, reductions of as much as 25% of anemia, 35% of iron deficiency anemia, and 73% of severe anemia could be realized.

In developed countries iron deficiency is generally the major cause of anemia. Data from the United States[3] showed that for each case of anemia, there were 2.5 cases of iron deficiency. There are, however, no data to show that this ratio applies to other parts of the world where iron deficiency is not always the only or primary cause of anemia.

Studies in Côte d'Ivoire[4] and Benin[5] estimated that iron deficiency anemia accounted for about 50% of the anemia observed. In the Côte d'Ivoire study, the proportion of anemic individuals with iron deficiency varied by age and sex. About 80% of the anemic preschool-age children had iron deficiency anemia, compared with 50% of the school-age children and women and 20% of the men. Malaria and other infections or inflammatory disorders contributed significantly to the high prevalence of anemia, particularly in young children, but these infections and/or disorders and iron deficiency could not explain all of the anemia cases.

Two studies used a technique called attributable risk analysis to estimate the proportion of anemia cases in the study population that can be attributed to hookworm and malaria. In the first study, carried out on the Kenyan coast,[6] 76% of the preschool-age children were anemic (Hb <110 g/L) and 3% severely so (Hb <50 g/L). Only 4%, 3%, and 7% of the anemia in the study population—***irrespective of whether the subjects had hookworm or not***—were attributed to, respectively, hookworm infection, heavy hookworm infection, and malaria. Among the ***children infected with hookworm in the study***, however, 14%, 28%, and 18% of the anemia cases could be explained by, respectively, hookworm infection, heavy hookworm infection, and malaria infection. Thus, in areas where the attributable risk of malaria or helminth infection to anemia is high, it is important to identify and treat these infections, especially in the most vulnerable segments of the population. The authors of the above study note that the low percentages attributable to malaria could be partially explained by the marked annual and seasonal variation in prevalence, which makes it difficult to capture the dynamic association between malaria and anemia. The same complexities apply in determining attributable proportions for helminth parasitemia and anemia.

In the second study involving attributable risk analysis, among Zanzibari schoolchildren,[7] 62% of the children were anemic, 3% were severely anemic, and 51% were iron-deficient anemic. The authors estimated that if hookworm infection could be eradicated, the prevalence of anemia could be reduced by as much as 25%, iron deficiency anemia by 35%, and severe anemia (Hb <70 g/L) by 73%. Ten percent or less of anemia and iron deficiency anemia was attributable to malaria, infection with the nematode ***Ascaris lumbricoides***, or stunting (a proxy indicator for a chronically poor diet).

A review of studies conducted between 1985 and 2000 among pregnant women in areas with ***Plasmodium falciparum*** malaria[8] estimated that the population-attributable risk range for this type of malaria in pregnant women was 2–15% for moderate (Hb<100–110 g/L) and severe (Hb<70–80 g/L) anemia.

Distinguishing between attributable risk for the entire population—whether or not infection is present—and attributable risk for infected individuals can be important for evaluating program effectiveness. For example, if iron-fortified wheat flour is introduced in a hookworm- or malaria-endemic area where no control programs are in place, the prevalence of anemia might not be reduced significantly at the population level, so the program would be deemed unsuccessful. However, among those who are iron-deficient anemic but not infected, the program could be effective.

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Summary

Anemia can be caused by iron deficiency or by other nutritional and health factors. The distinction between causes is important for two reasons:

- Hemoglobin measurements are important in diagnosing anemia, but they are neither sensitive to nor specific to iron deficiency.
- The success of any intervention to correct and control anemia depends on whether the intervention deals with the underlying causes. In many developing countries, it is unlikely that all anemia results from iron deficiency, because other nutritional deficiencies as well as malaria, heavy loads of some helminths, and other inflammatory/infectious diseases also cause anemia.

Knowing the underlying causes of anemia will enable program managers to identify which interventions need to be implemented to reduce the unacceptably high prevalence of anemia in many countries. Where most of the anemia is not the result of iron deficiency, iron supplementation or the fortification of food with iron will be inadequate by themselves to prevent and control anemia.

Where most anemia in a population is not the result of iron deficiency, iron supplementation or the fortification of food with iron by themselves will be inadequate to prevent and control anemia.

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About INACG

The International Nutritional Anemia Consultative Group (INACG) is dedicated to reducing the prevalence of iron deficiency anemia and other nutritionally preventable anemias worldwide. It sponsors international meetings and scientific reviews and convenes task forces to analyze issues related to etiology, treatment, and prevention of nutritional anemias. Examination of these issues is important to the establishment of public policy and action programs.

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